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<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> <p>(21) International Application Number: PCT/US00/11531</p> <p>(22) International Filing Date: 28 April 2000 (28.04.00)</p> <p>(30) Priority Data: 60/134,139 14 May 1999 (14.05.99) US</p> <p>(71) Applicant: ORTHO-MCNEIL PHARMACEUTICAL, INC. [US/US]; U.S. Route 202, Raritan, NJ 08869-0602 (US).</p> <p>(72) Inventor: BULLINGTON, James; 21 Wesleyan Drive, Hamilton Square, NJ 08690 (US).</p> <p>(74) Agents: CIAMPORCERO, Audley, A. et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933 (US).</p> </td> <td style="width: 50%; vertical-align: top; padding: 5px;"> <p>(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> </td> </tr> </table>			<p>(21) International Application Number: PCT/US00/11531</p> <p>(22) International Filing Date: 28 April 2000 (28.04.00)</p> <p>(30) Priority Data: 60/134,139 14 May 1999 (14.05.99) US</p> <p>(71) Applicant: ORTHO-MCNEIL PHARMACEUTICAL, INC. [US/US]; U.S. Route 202, Raritan, NJ 08869-0602 (US).</p> <p>(72) Inventor: BULLINGTON, James; 21 Wesleyan Drive, Hamilton Square, NJ 08690 (US).</p> <p>(74) Agents: CIAMPORCERO, Audley, A. et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933 (US).</p>	<p>(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
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<p>(54) Title: SUBSTITUTED 3-PYRIDYL-4-ARYLPYRROLES, AND RELATED THERAPEUTIC AND PROPHYLACTIC METHODS</p> <div style="text-align: center; margin: 20px 0;"> <p style="margin-left: 400px;">(I)</p> </div> <p>(57) Abstract</p> <p>This invention provides novel substituted 3-pyridyl-4-arylpyrroles, having chemical structure (I) and pharmaceutical compositions comprising same, useful for treating disorders ameliorated by reducing TNF-α production and/or p38 activity in appropriate cells. This invention also provides therapeutic and prophylactic methods using the instant pharmaceutical compositions.</p>				

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**SUBSTITUTED 3-PYRIDYL-4-ARYLPYRROLES, AND RELATED
THERAPEUTIC AND PROPHYLACTIC METHODS**

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Field of the Invention

This invention relates to novel substituted 3-pyridyl-4-arylpyrroles and their therapeutic and prophylactic uses. Disorders treated and/or prevented using these compounds include inflammatory and AIDS-related disorders.

Background of the Invention

TNF- α and p38-Related Disorders

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Inflammatory cytokines such as TNF- α are produced via the activity of kinases. Such kinases include the Cytokine Suppressive Antiinflammatory Drug-Binding Protein (CSBP)/p38 kinase, a Mitogen-Activated Protein (MAP) kinase family of serine-threonine protein kinases. Inflammatory cytokines play an important role in a number of inflammatory disorders (1), neurodegenerative disorders (10), and AIDS-related disorders (11-14). Although the precise mechanism of kinases such as p38 is unknown, p38 has been implicated in both the production of TNF- α and the signaling responses associated with the TNF- α receptor (6).

Arthritis is a prime example of an inflammatory disorder, and is thus the inflammatory disorder focused on most in this section. Arthritis affects millions of people and can strike at any joint in the human body. Its symptoms range from mild pain and inflammation in affected joints, to severe and debilitating pain and inflammation. Although the disorder is associated mainly with aging adults, it is not restricted to adults.

The most common rheumatoid arthritis therapy involves the use of nonsteroidal anti-inflammatory drugs (NSAID's) to alleviate symptoms. However, despite the widespread use of NSAID's, many individuals cannot tolerate the doses necessary to treat the disorder over a prolonged period of

time. In addition, NSAID's merely treat the symptoms of disorder without affecting the underlying cause.

Other drugs such as methotrexate, gold salts, D-penicillamine and prednisone are often used when patients fail to respond to NSAID's. These drugs also have significant toxicities and their mechanism of action remains unknown. Monoclonal antibodies to TNF- α and receptor antagonists to interleukin 1 β (IL-1 β) have been shown to reduce symptoms of rheumatoid arthritis in small-scale human clinical trials (2).

In addition to protein-based therapies, there are small molecule agents that inhibit the production of these cytokines and have demonstrated activity in animal rheumatoid arthritis models (3). Of these small molecule agents, SB 203580 has proven effective in reducing the production of TNF- α and IL-1 β in lipopolysaccharide (LPS)-stimulated human monocyte cell lines with IC₅₀ values of 50 to 100 nM (4).

In addition to in vitro testing results, SB 203580 has been shown to inhibit the production of inflammatory cytokines in rats and mice at IC₅₀ values of 15 to 25 mg/kg (5). SB 203580 reduces the production of inflammatory cytokines by inhibiting the activity of CSBP/p38 kinase at an IC₅₀ of 200 nM (6). Due to SB 203580's oral activity and potency in animal models, researchers have suggested that a compound with such an activity profile has potential as a viable treatment for rheumatoid arthritis (5).

Pyridylpyrroles and their analogs have also been prepared as cytokine inhibitors and glucagon antagonists (7), and specifically as inhibitors of IL-1 β , TNF- α and other cytokines. Arylpyrroles (8) and triarylpyrroles (9) have also been prepared as cytokine inhibitors.

The role of CSBP/p38 has been implicated recently in various neurodegenerative and AIDS-related disorders. With regard to neurodegenerative disorders, p38 has been shown to have a role in

determining whether a cell survives or undergoes neuronal programmed cell death or apoptosis (10, 11).

- Also related to AIDS, the Kaposi's sarcoma-associated herpesvirus
- 5 HHV8 has been shown to encode a G protein-coupled receptor that activates p38. It has been proposed that this activation contributes to tumorigenesis and angiogenesis leading to Kaposi's sarcoma (12).

- Associated with AIDS is the rapid activation of p38 induced by infection
- 10 of a CCR5⁺ human T cell line by SIV, suggesting that p38 may play a role in early viral infection (13). Additionally, p38 inhibitors have been shown to block HIV replication in vitro in a manner that may be TNF- α -independent (14).

Absence of Clinically Effective Agents

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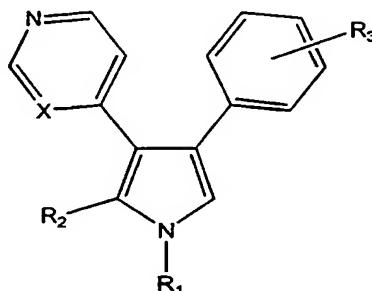
- In general, arthritis -- particularly rheumatoid arthritis -- and the host of other inflammatory and AIDS-related disorders all take a severe toll on those afflicted. There is a tremendous need for small molecule agents to treat these disorders. To date, however, no such agents have ever been identified and
- 20 shown to be clinically effective in humans.

Summary of the Invention

This invention provides a compound having the structure:

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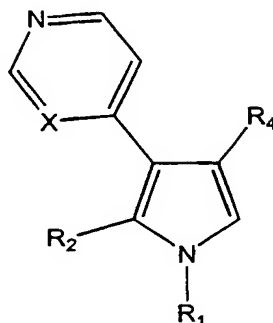


or a pharmaceutically acceptable salt thereof, wherein:

- (a) R_1 is selected from the group consisting of (i) hydrogen, (ii) C_{1-5} alkyl, (iii) substituted or unsubstituted C_{1-5} alkylamino, (iv) N-containing C_{1-5} alkyl heterocycle selected from thiazolidine, piperidine, morpholine, piperazine, thiomorpholine, pyrrolidine, thiazine, pyrrole and imidazole, (v) phenyl, (vi) phenyl independently substituted with one or more of C_{1-5} alkyl, amino, substituted amino, nitro, nitrile and sulfone, and (vii) pyridine;
- (b) R_2 is selected from the group consisting of (i) hydrogen, (ii) $(CH_2)_3OH$, (iii) substituted or unsubstituted C_{1-5} alkyl phenyl, and (iv) N-containing C_{1-5} alkyl heterocycle selected from thiazolidine, piperidine, morpholine, piperazine, thiomorpholine, pyrrolidine, thiazine, pyrrole and imidazole;
- (c) R_3 is one or more substituents independently selected from the group consisting of hydrogen, halogen, methoxy, nitro, trifluoromethyl, hydroxy, dimethylamino and methylsulfoxide; and
- (d) X is either C or N.

This invention also provides a second compound having the structure:

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or a pharmaceutically acceptable salt thereof, wherein:

- (a) R_1 is selected from the group consisting of (i) hydrogen, (ii) C_{1-5} alkyl, (iii) substituted or unsubstituted C_{1-5} alkylamino, (iv) N-containing C_{1-5} alkyl heterocycle selected from thiazolidine, piperidine, morpholine, piperazine, thiomorpholine, pyrrolidine, thiazine, pyrrole and imidazole, (v) phenyl, (vi) phenyl independently substituted with one or more of C_{1-5} alkyl, amino, substituted amino, nitro, nitrile and sulfone, and (vii) pyridine;
- (b) R_2 is selected from the group consisting of (i) hydrogen, (ii) $(CH_2)_3OH$, (iii) substituted or unsubstituted C_{1-5} alkyl phenyl, and (iv) N-containing C_{1-5} alkyl heterocycle selected from thiazolidine, piperidine, morpholine, piperazine, thiomorpholine, pyrrolidine, thiazine, pyrrole and imidazole;
- (c) R_4 is a substituted or unsubstituted heterocycle selected from pyridine, pyrimidine, furan or thiophene; and,
- (d) X is either C or N.

This invention further provides a pharmaceutical composition comprising one of the instant compounds and a pharmaceutically acceptable carrier.

This invention still further provides a method of treating a subject having a disorder ameliorated by reducing $TNF-\alpha$ production and/or p38 activity in

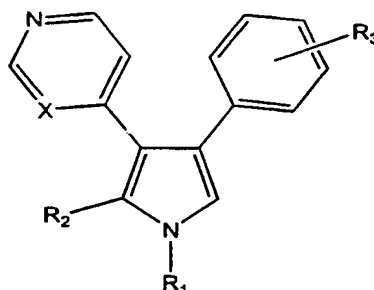
appropriate cells, which comprises administering to the subject a therapeutically effective dose of the instant pharmaceutical composition.

- Finally, this invention provides a method of preventing an inflammatory
- 5 response in a subject, comprising administering to the subject a prophylactically effective amount of the instant pharmaceutical composition either preceding or subsequent to an event anticipated to cause the inflammatory response in the subject.

Detailed Description of the Invention

This invention provides novel substituted 3-pyridyl-4-arylpyrroles. These compounds have surprising usefulness in treating disorders ameliorated by a reduction in TNF- α production and/or p38 activity, and are therefore useful for treating inflammatory disorders such as rheumatoid arthritis, as well as AIDS-related disorders.

Specifically, this invention provides a first compound having the structure:



or a pharmaceutically acceptable salt thereof, wherein:

- (a) R_1 is selected from the group consisting of (i) hydrogen, (ii) C_{1-5} alkyl, (iii) substituted or unsubstituted C_{1-5} alkylamino, (iv) N-containing C_{1-5} alkyl heterocycle selected from thiazolidine, piperidine, morpholine, piperazine, thiomorpholine, pyrrolidine, thiazine, pyrrole and imidazole, (v) phenyl, (vi) phenyl independently substituted with one or more of C_{1-5} alkyl, amino, substituted amino, nitro, nitrile and sulfone, and (vii) pyridine;
- (b) R_2 is selected from the group consisting of (i) hydrogen, (ii) $(CH_2)_3OH$, (iii) substituted or unsubstituted C_{1-5} alkyl phenyl, and (iv) N-containing C_{1-5} alkyl heterocycle selected from thiazolidine, piperidine, morpholine, piperazine, thiomorpholine, pyrrolidine, thiazine, pyrrole and imidazole;

- (c) R₃ is one or more substituents independently selected from the group consisting of hydrogen, halogen, methoxy, nitro, trifluoromethyl, hydroxy, dimethylamino and methylsulfoxide; and
- (d) X is either C or N.

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In one embodiment of the first compound:

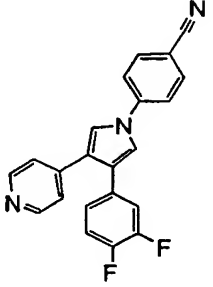
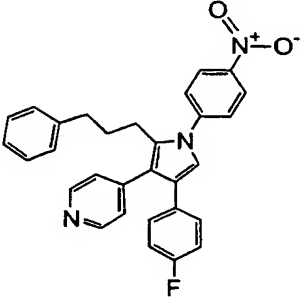
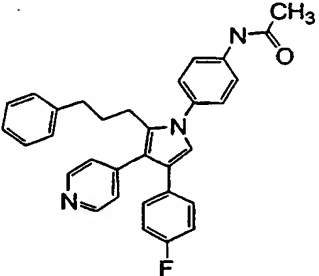
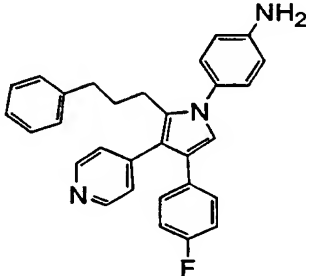
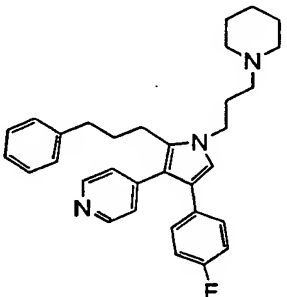
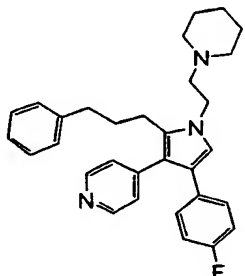
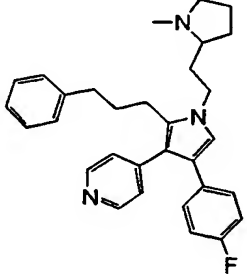
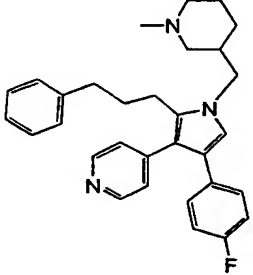
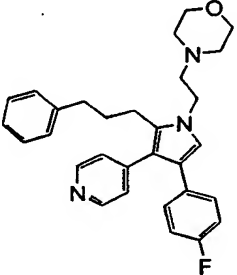
- (a) R₁ is selected from the group consisting of (i) hydrogen, (ii) C₁₋₅alkyl, (iii) substituted or unsubstituted C₁₋₅alkylamino, (iv) N-containing C₁₋₅alkyl heterocycle selected from piperidine, morpholine and pyrrolidine, and (v) phenyl substituted with a substituent selected from the group consisting of amino, substituted amino, nitro and nitrile;
- (b) R₂ is selected from the group consisting of hydrogen and (CH₂)₃phenyl;
- (c) R₃ is selected from the group consisting of halogen, nitro and trifluoromethyl; and
- (d) X is C.

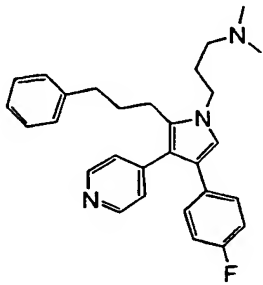
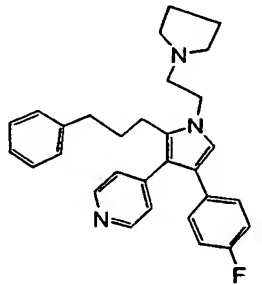

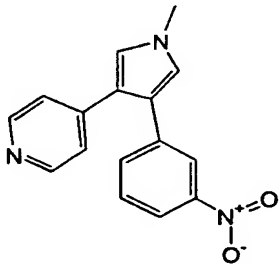
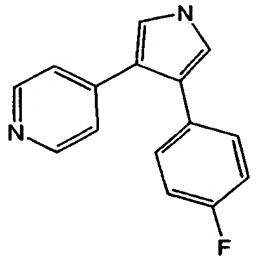
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In the preferred embodiment, the first compound is selected from the group of compounds shown in Table 1.

Table 1

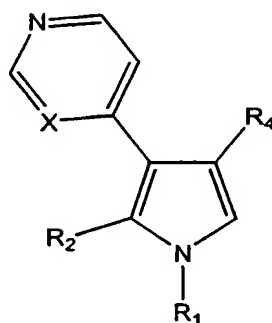
		
Compound 4	Compound 31	Compound 32
		
Compound 33	Compound 39	Compound 40
		
Compound 41	Compound 42	Compound 43

		
Compound 44	Compound 45	Compound 7
		
Compound 11	Compound 27	

This invention also provides a second compound having the structure:

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or a pharmaceutically acceptable salt thereof, wherein:

- (a) R_1 is selected from the group consisting of (i) hydrogen, (ii) C_{1-5} alkyl, (iii) substituted or unsubstituted C_{1-5} alkylamino, (iv) N-containing C_{1-5} alkyl heterocycle selected from thiazolidine, piperidine, morpholine, piperazine, thiomorpholine, pyrrolidine, thiazine, pyrrole and imidazole,

- (v) phenyl, (vi) phenyl independently substituted with one or more of C₁₋₅alkyl, amino, substituted amino, nitro, nitrile and sulfone, and (vii) pyridine;
- (b) R₂ is selected from the group consisting of (i) hydrogen, (ii) (CH₂)₃OH, 5 (iii) substituted or unsubstituted C₁₋₅alkyl phenyl, and (iv) N-containing C₁₋₅alkyl heterocycle selected from thiazolidine, piperidine, morpholine, piperazine, thiomorpholine, pyrrolidine, thiazine, pyrrole and imidazole;
- (c) R₄ is a substituted or unsubstituted heterocycle selected from pyridine, pyrimidine, furan or thiophene; and,
- 10 (d) X is either C or N.

In one embodiment of the second compound:

- (a) R₁ is selected from the group consisting of (i) C₁₋₅alkyl, (ii) substituted or 15 unsubstituted C₁₋₅alkylamino, (iii) substituted or unsubstituted C₁₋₅alkyl heterocyclic amino, (iv) phenyl, and (v) phenyl independently substituted with one or more of amino, substituted amino, nitro or nitrile;
- (b) R₂ is selected from the group consisting of hydrogen and (CH₂)₃phenyl; and
- (c) X is C.

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The instant compounds can be isolated and used as free bases. They can also be isolated and used as pharmaceutically acceptable salts. Examples of such salts include hydrobromic, hydroiodic, hydrochloric, perchloric, sulfuric, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, 25 hydroethanesulfonic, benzenesulfonic, oxalic, palmoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic and saccharic.

This invention further provides a pharmaceutical composition comprising one of the instant compounds and a pharmaceutically acceptable carrier.

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Pharmaceutically acceptable carriers are well known to those skilled in the art and include, but are not limited to, from about 0.01 to about 0.1 M and preferably 0.05 M phosphate buffer or 0.8% saline. Such pharmaceutically acceptable carriers can be aqueous or non-aqueous solutions, suspensions and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, ethanol, alcoholic/aqueous solutions, glycerol, emulsions or suspensions, including saline and buffered media. Oral carriers can be elixirs, syrups, capsules, tablets and the like. The typical solid carrier is an inert substance such as lactose, starch, glucose, methyl-cellulose, magnesium stearate, dicalcium phosphate, mannitol and the like. Parenteral carriers include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's and fixed oils. Intravenous carriers include fluid and nutrient replenishers, electrolyte replenishers such as those based on Ringer's dextrose and the like. Preservatives and other additives can also be present, such as, for example, antimicrobials, antioxidants, chelating agents, inert gases and the like. All carriers can be mixed as needed with disintegrants, diluents, granulating agents, lubricants, binders and the like using conventional techniques known in the art.

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This invention still further provides a method of treating a subject having a disorder ameliorated by reducing TNF- α production and/or p38 activity in appropriate cells, which comprises administering to the subject a therapeutically effective dose of the instant pharmaceutical composition.

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In one embodiment, the disorder is an inflammatory disorder. In another embodiment, the disorder is an AIDS-related disorder. Examples of disorders treatable by the instant pharmaceutical composition include, without limitation, rheumatoid arthritis, osteoporosis, osteoarthritis, allergic inflammation, periodontal disorder, inflammatory bowel disorder, septic shock, insulin-dependent diabetes mellitus, non-insulin-dependent diabetes, cachexia, pulmonary fibrosis, myasthenia gravis, Crohn's disease, hepatitis, primary biliary cirrhosis, acute pancreatitis, allograft rejection, glioblastoma, alopecia

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areta, psoriasis, ischemia, congestive heart failure, restenosis, atherosclerosis, systemic lupus erythematosus, nephritis, Guillain-Barre Syndrome, viral myocarditis, HIV replication, T-cell depletion in HIV infection, cognitive deficits induced by neuronal inflammation, multiple sclerosis, stroke, neuropathic pain, 5 HIV dementia and Alzheimer's disease. In the preferred embodiment, the disorder is rheumatoid arthritis.

As used herein, the term "subject" includes, without limitation, any animal or artificially modified animal having a disorder ameliorated by reducing TNF- α 10 production and/or p38 activity in appropriate cells. In the preferred embodiment, the subject is a human.

As used herein, "appropriate cells" include, by way of example, cells which secrete or are capable of secreting TNF- α , and cells wherein p38 has 15 been activated. Specific examples of appropriate cells include, without limitation, monocytes, macrophages, T lymphocytes, fibroblasts, dendritic cells, Langerhans cells, Kupffer cells and astroglial cells.

Administering the instant pharmaceutical composition can be effected or 20 performed using any of the various methods known to those skilled in the art. The instant compounds can be administered, for example, intravenously, intramuscularly, orally and subcutaneously. In the preferred embodiment, the instant pharmaceutical composition is administered orally. Additionally, administration can comprise giving the subject a plurality of dosages over a 25 suitable period of time. Such administration regimens can be determined according to routine methods.

As used herein, a "therapeutically effective dose" of a pharmaceutical composition is an amount sufficient to stop, reverse or reduce the progression 30 of a disorder. A "prophylactically effective dose" of a pharmaceutical composition is an amount sufficient to prevent a disorder, i.e., eliminate, ameliorate and/or delay the disorder's onset. Methods are known in the art for determining therapeutically and prophylactically effective doses for the instant

pharmaceutical composition. The effective dose for administering the pharmaceutical composition to a human, for example, can be determined mathematically from the results of animal studies.

5 In one embodiment, the therapeutically and/or prophylactically effective dose is a dose sufficient to deliver from about 0.05 mg/kg of body weight to about 200 mg/kg of body weight of the instant pharmaceutical composition. In another embodiment, the therapeutically and/or prophylactically effective dose is a dose sufficient to deliver from about 0.5 mg/kg of body weight to about 50
10 mg/kg of body weight. More specifically, in one embodiment, oral doses range from about 0.05 mg/kg to about 100 mg/kg daily. In another embodiment, oral doses range from about 0.05 mg/kg to about 50 mg/kg daily, and in a further embodiment, from about 0.05 mg/kg to about 20 mg/kg daily. In yet another embodiment, infusion doses range from about 1.0 μ g/kg/min to about 1.0×10^4
15 μ g/kg/min of inhibitor, admixed with a pharmaceutical carrier over a period ranging from about several minutes to about several days. In a further embodiment, for topical administration, the instant compound can be combined with a pharmaceutical carrier at a drug/carrier ratio of from about 0.001 to about 0.1.

20

 This invention still further provides a method of preventing an inflammatory response in a subject, comprising administering to the subject a prophylactically effective amount of the instant pharmaceutical composition either preceding or subsequent to an event anticipated to cause the
25 inflammatory response in the subject. In the preferred embodiment, the event is an insect sting or an animal bite.

 As used herein, the following chemical terms shall have the meanings as set forth in this paragraph: "independently", when in reference to chemical
30 substituents, shall mean that when more than one substituent exists, the substituents may be the same or different; "alkyl" shall mean straight, cyclic and branched-chain alkyl; "alkoxy" shall mean O-alkyl; "halogen" shall mean fluorine, chlorine, bromine or iodine; "Ph" shall mean phenyl; "TCA" shall mean

trichloroacetic acid; "FCS" shall mean fetal calf serum; and "RPMI" shall mean the medium from the Roswell Park Memorial Institute (Sigma cat # R0833).

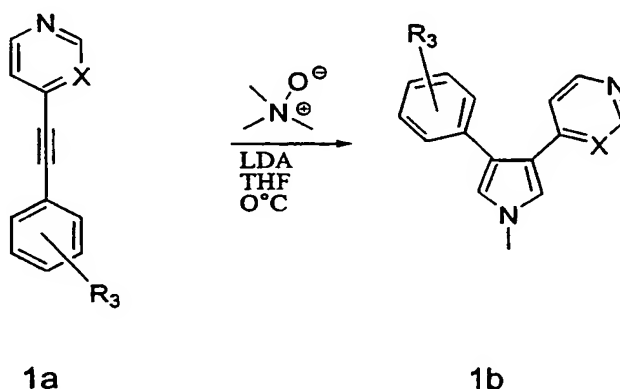
This invention will be better understood by reference to the Experimental
5 Details which follow, but those skilled in the art will readily appreciate that these
are only illustrative of the invention as described more fully in the claims which
follow thereafter. Additionally, throughout this application, various publications
are cited. The disclosure of these publications is hereby incorporated by
reference into this application to describe more fully the state of the art to which
10 this invention pertains.

Experimental Details

I. General Synthetic Schemes

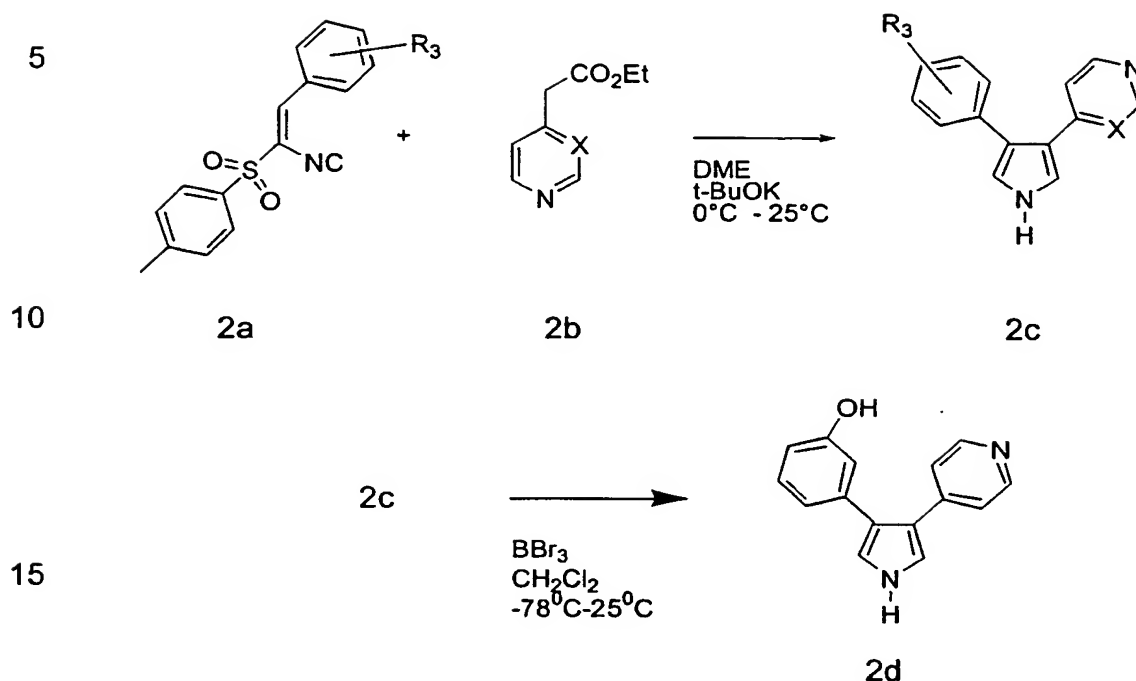
5 Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below and illustrated in the following general schemes. The products of some schemes can be used as intermediates to produce more than one of the instant compounds. In those cases, the choice of intermediates to be used to produce
10 subsequent compounds of the present invention is a matter of discretion that is well within the capabilities of those skilled in the art.

Scheme 1

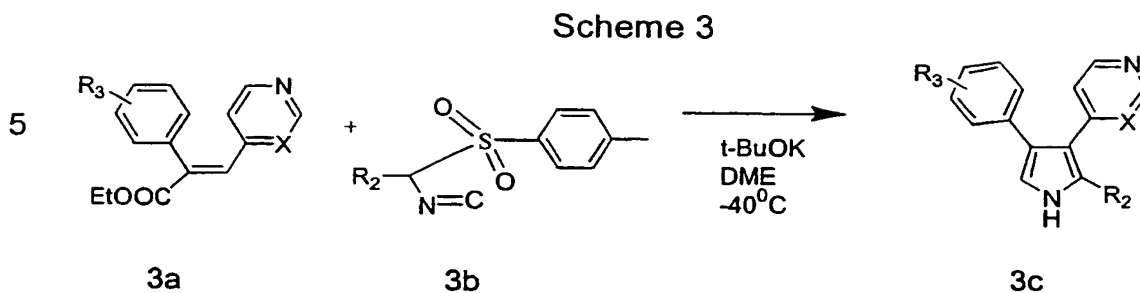


15 Scheme 1 can be used to produce the compounds of the invention
where R₁ is methyl. Compound 1a, such as a 1,2-disubstituted alkyne, can be
used as the starting material for Scheme 1. 1,2-disubstituted alkynes can be
prepared following known procedures. The substituents X and R₃ of the
compounds of the invention are determined by the substituents of Compound
20 1a. Compound 1a is combined with trimethylamine-N-oxide and dissolved in a
dry solvent, such as THF, and cooled to 0°C. A base, such as lithium
diisopropylamide, is added and the reaction is stirred at 0°C for 1 h to give
Compound 1b as the product.

Scheme 2



Scheme 2 can be used to prepare compounds of the invention where R₁ is hydrogen. Compound 2a, of the type 1-[(1-isocyano-2-(3-methoxyphenyl)ethenyl)sulfonyl]-4-methylbenzene can be used as the starting material for Scheme 2. Compound 2a can be prepared following known procedures. The substituent R₃ of the compounds of the invention are generally determined by the substituents on the phenyl of the ethynyl group in Compound 2a; the X atom is determined by the heteroaromatic substituent of the acetate group in Compound 2b. Compound 2a is dissolved in a dry solvent, such as ethylene glycol dimethyl ether, and added dropwise to a mixture of Compound 2b, such as ethyl 4-pyridylacetate, and a base, such as potassium t-butoxide, in a dry solvent, such as ethylene glycol dimethyl ether, at 0°C. After the addition is complete, the reaction is warmed to 25°C and stirred for 3 h to give the intermediate Compound 2c. When R₃ is methoxy, the intermediate Compound 2c can be treated with a demethylating agent, such as BBr₃, in an inert solvent, such as CH₂Cl₂, at -78°C to give Compound 2d.



10

Scheme 3 can be used to produce the compounds of the invention where R_1 is hydrogen and R_2 is substituted or unsubstituted. Compound 3a, a diaryl substituted α,β -unsaturated ester, can be used as the starting material for Scheme 3. Compounds of this type can be prepared following known procedures. Compound 3b can be the other starting material, a substituted

15

known procedures.

For example, Compound 3a can be ethyl 4-fluoro- α -[(4-pyridyl)methylene]benzeneacetic acid and Compound 3b can be 1-(4-tolylsulfonyl)-1-(3-phenylpropyl)methyl isocyanide. Compound 3a and Compound 3b are dissolved in dry solvent, such as ethylene glycol dimethyl ether, and added dropwise to a -40°C mixture of a base, such as potassium t-butoxide, in a dry solvent, such as ethylene glycol dimethyl ether. Stirring at -40°C is continued for 1 hour before allowing the temperature to rise to -20°C . Accordingly, the resulting Compound 3c is 4-(4-fluorophenyl)-2-(3-phenylpropyl)-3-(4-pyridyl)pyrrole (Compound 27).

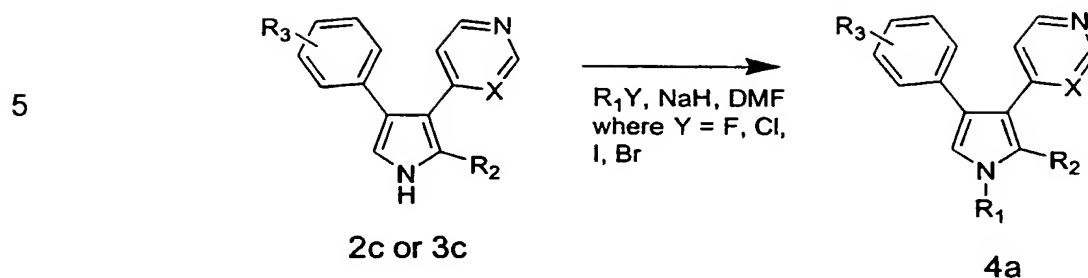
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25

As shown in Scheme 4, Compound 2c and Compound 3c can be used as intermediates to form other compounds of the present invention.

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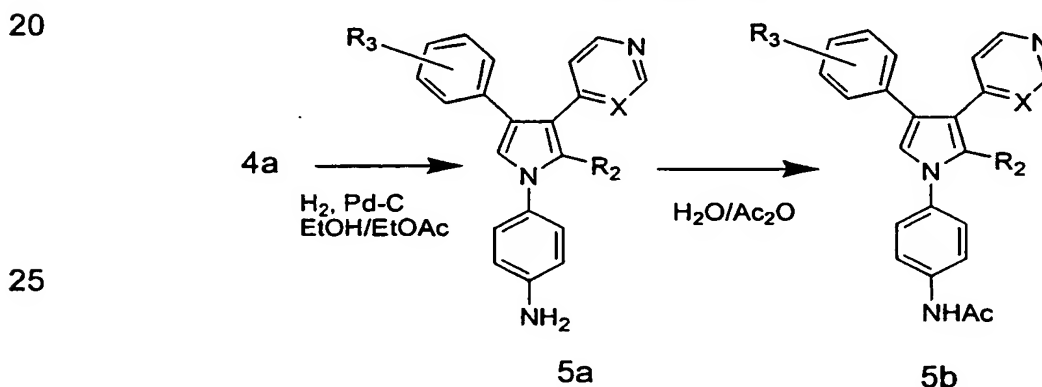
Scheme 4



10 Scheme 4 can be used to produce the compounds of the invention where R_1 is substituted. Intermediate Compound 2c or Compound 3c is added portionwise to a base, such as sodium hydride, in a solvent, such as dimethylformamide, at 0°C. After the addition is complete, the reaction is stirred at 0°C an additional 15 minutes followed by portionwise addition of an

15 alkylating agent, such as 4-(2-chloroethyl)morpholine hydrochloride. The reaction is heated to 60°C for 16 hours before the temperature is allowed to cool to 25°C to produce Compound 4a.

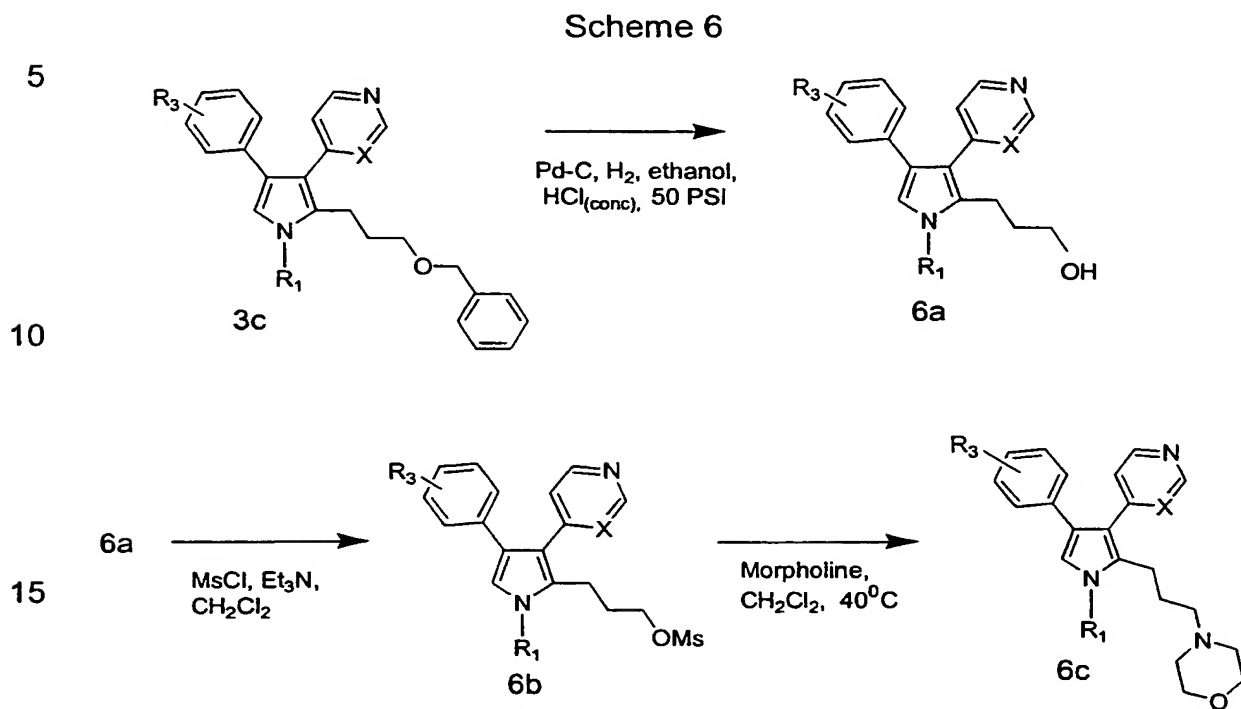
Scheme 5



25

30 Scheme 5 can be used to produce the compounds of the invention where R_1 is substituted. When R_1 is 4-nitrophenyl, the intermediate Compound 4a can be reduced using a catalyst, such as palladium on carbon in a solvent, such as ethyl acetate, to give Compound 5a. The amine Compound

5a can be treated with an acylating agent, such as acetic anhydride, in a solvent, such as water, to give the product Compound 5b.



20 Scheme 6 can be used to produce the compounds of the invention where R_2 is an alkyl chain containing heteroatoms. Intermediate Compound 3c is exposed to reducing conditions using a catalyst, such as palladium on carbon in a solvent, such as ethanol, to which a catalytic amount of acid, such as concentrated hydrochloric acid, is added to give Compound 6a. The alcohol

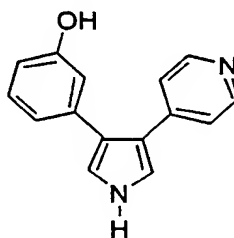
25 Compound 6a can be treated with an sulfonating agent, such as mesyl chloride, and a base, such as triethylamine, in a solvent, such as CH_2Cl_2 , to give the intermediate Compound 6b. Compound 6b can then be heated with a nucleophile, such as morpholine, in a solvent, such as CH_2Cl_2 , to give Compound 6c.

II. Specific Compound Syntheses

Specific compounds which are representative of this invention can be prepared as per the following examples. No attempt has been made to optimize the yields obtained in these reactions. Based on the following, however, one skilled in the art would know how to increase yields through routine variations in reaction times, temperatures, solvents and/or reagents.

The products of certain syntheses can be used as intermediates to produce more than one of the instant compounds. In those cases, the choice of intermediates to be used to produce compounds of the present invention is a matter of discretion that is well within the capabilities of those skilled in the art.

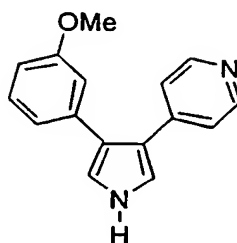
Compound 12



3-(3-hydroxyphenyl)-4-(4-pyridyl)pyrrole hydrobromide

Compound 13 (0.15 g, 0.006 mol) was dissolved in CH_2Cl_2 (50 mL) and cooled to -78°C . The mixture was stirred for 16 h, allowing the temperature to warm to 25°C . The reaction was quenched with MeOH (20 mL) and evaporated to a solid. The solid was triturated with ether and filtered to give Compound 12 (0.15 g, 79% yield). ^1H NMR (DMSO- d_6) δ 11.91 (1H, s, NH), 9.47 (1H, br s, OH), 8.66 (2H, d, $J = 8.6$), 7.86-7.86 (3H, m), 7.25-7.14 (1H, m) 7.06 (1H, s) 6.80-6.66 (3H, m).

Compound 13



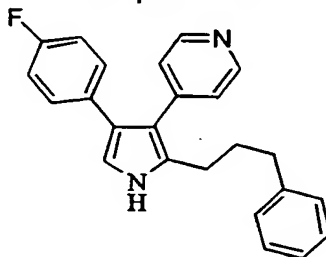
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3-(3-methoxyphenyl)-4-(4-pyridyl)pyrrole

1-[(1-isocyano-2-(3-methoxyphenyl)ethenyl)sulfonyl]-4-methylbenzene (9.0 g, 0.0285 mol) was dissolved in dry DME (200 mL) and added dropwise to a cooled (0°C) mixture of ethyl 4-pyridylacetate (9.0 g, 0.545 mol) and potassium t-butoxide (7.1 g, 0.0633 mol) in dry DME (100 mL). After the addition was complete the reaction was warmed to 25°C and stirred for 3 h. The reaction was then poured into ice water (1200 mL) and extracted into CH₂Cl₂ (3 X 500 mL). The combined organics were dried over Na₂SO₄, filtered and evaporated in vacuo to give a solid. This solid was then triturated with ether and filtered to give 3.0 g of pure 3-(3-methoxyphenyl)-4-(4-pyridyl)pyrrole. The filtrate was again evaporated in vacuo and then triturated with a 50/50 mixture of CH₂Cl₂ and ether to give an additional 1.5 g of pure product. Finally the filtrate was evaporated in vacuo and purified on SiO₂ eluting with ethyl acetate to give another 0.5 g of pure product resulting in a 70% combined yield. ¹HNMR (DMSO-d₆) δ 11.38 (1H, br s, NH), 8.37 (2H, d, J = 6.1), 7.24-7.17 (4H, m), 7.02-7.00 (1H, m), 6.80-6.77 (3H, m), 3.68 (3H, s).

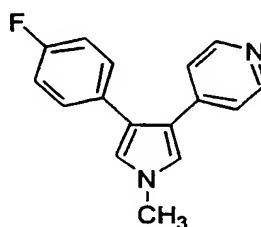
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Compound 27

4-(4-fluorophenyl)-2-(3-phenylpropyl)-3-(4-pyridyl)pyrrole

1-(4-tolylsulfonyl)-1-(3-phenylpropyl)methyl isocyanide (10.9 g, 0.0346 mol) and ethyl 4-fluoro- α -[(4-pyridyl)methylene]benzeneacetic acid (9.4 g, 0.0346 mol) were dissolved in dry DME (250 mL) and added dropwise to a cooled (-40°C) mixture of potassium t-butoxide (9.5 g, 0.0847 mol) in dry DME (50 mL). The mixture was stirred for 1 hour allowing the temperature to rise to -20°C. The mixture was poured into H₂O (1800 mL) and extracted into CH₂Cl₂ (3 X 500 mL). The combined organics were dried over Na₂SO₄ and evaporated in vacuo to give a solid. Trituration of the solid with acetonitrile gave pure Compound 27 (6.0 g, 49% yield). ¹HNMR (DMSO-d₆) δ 11.17 (1H, s, NH), 8.38 (2H, d, J = 5.8 Hz), 7.27-6.92 (12H, m), 2.61-2.51 (4H, m), 1.93-1.83 (2H, m).

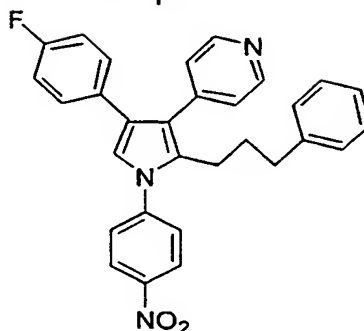
Compound 28



1-methyl-3-(4-fluorophenyl)-4-(4-pyridyl)pyrrole

4-[(4-fluorophenyl)ethynyl]pyridine (2.0 g, 0.0101 mol) and trimethylamine-N-oxide (1.0 g, 0.0133 mol) were dissolved in dry THF (200 mL) and cooled to 0°C. Lithium diisopropylamide (1.5M in THF, 14 mL) was added and the reaction was stirred at 0°C for 1 h. The reaction was then quenched with H₂O (20 mL) and extracted into CH₂Cl₂ (2X100 mL). The organics were dried over Na₂SO₄ and evaporated in vacuo to give an oil. Purification on SiO₂ eluting with EtOAc gave 0.356 g (14% yield) of Compound 28. ¹HNMR (CDCl₃) δ 8.41 (2H, d, J=5.4 Hz), 7.19 (2H, dd, J = 5.7, 6.0 Hz), 7.11 (2H, d, J = 5.4 Hz), 6.99 (2H, dd, J=8.7, 8.5 Hz), 6.87 (1H, d, J = 2.1 Hz), 6.69 (1H, d, J = 2.4 Hz), 3.71 (3H, s).

Compound 30

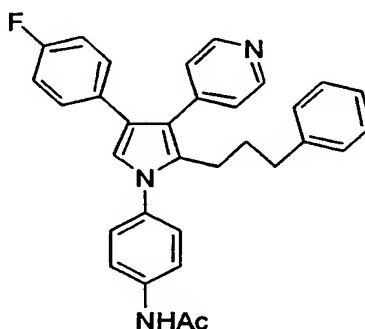


5 4-(4-fluorophenyl)-1-(4-nitrophenyl)-2-(3-phenylpropyl)-3-(4-pyridyl)pyrrole

Sodium hydride (60% in mineral oil, 0.80 g, 0.0209 mol) was washed 3 times with hexane and then dissolved in DMF (15 mL). Compound 27 (6.0 g, 0.01683 mol) was then added portionwise at 0°C with stirring. After the addition was complete, the reaction was stirred at 0°C an additional 15 minutes
 10 followed by dropwise addition of 4-fluoronitrobenzene (2.4 g, 0.170 mol). The reaction was stirred at 0°C for 1 h before the temperature was allowed to warm to 25°C. The reaction was poured into 1.5 L of water and extracted into CH₂Cl₂ (3 X 500 mL). The combined organics were washed with water (4 X 500 mL) and dried over Na₂SO₄. Evaporation *in vacuo* gave a yellow solid
 15 which was triturated with acetonitrile, filtered and air dried to give 6.6 g (82.5 % yield) of pure Compound 30. ¹HNMR (CDCl₃) δ 8.52 (2H, d, J = 5.8 Hz), 8.26 (2H, d, J = 8.9 Hz), 7.46 (2H, d, J = 8.9 Hz), 7.16-7.13 (3H, m), 7.09-7.03 (4H, m), 6.95-6.82 (5H, m) 2.73-2.67 (2H, m), 2.35-2.32 (2H, m), 1.53-1.43 (2H, m).

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Compound 31

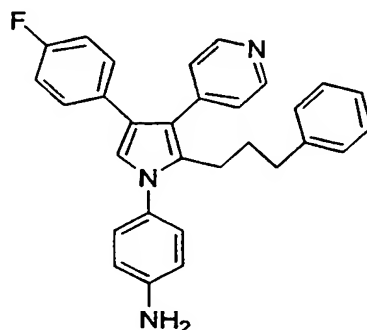


1-(4-acetoaminophenyl)-4-(4-fluorophenyl)-2-
(3-phenylpropyl)-3-(4-pyridyl)pyrrole

25

Compound 32 (0.85 g, 0.0019 mol) was stirred for 16 hours in acetic anhydride (20 mL) and H₂O (50 mL). The solution was extracted into ethyl acetate (100 mL), washed with H₂O (3 X 50 mL), then washed with saturated sodium bicarbonate (3 X 50 mL) and then washed again with H₂O (2 X 50 mL). The organics were dried over Na₂SO₄ and evaporated in vacuo to give Compound 31 (0.89 g, 96% yield) isolated as an oil. ¹HNMR (CDCl₃) δ 8.41 (2H, d, J = 5.6 Hz), 8.05 (1H, s), 7.73 (2H, d, J = 8.6 Hz), 7.28 (2H, d, J = 8.7 Hz), 7.17-7.04 (7H, m), 6.91-6.85 (4H, m), 6.79 (1H, s), 2.66-2.61 (2H, m), 2.35-2.30 (2H, m), 2.22 (3H, s), 1.59-1.51 (2H, m).

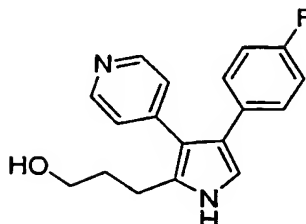
Compound 32



15 1-(4-aminophenyl)-4-(4-fluorophenyl)-2-(3-phenylpropyl)-3-(4-pyridyl)pyrrole

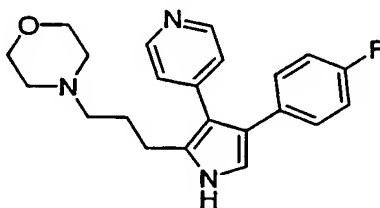
Compound 30 (6.6 g, 0.0138 mol) was suspended in ethanol (200 mL) and ethyl acetate (50 mL) and exposed to reducing conditions for 16 hours on a Parr hydrogenator at 50 PSI. The mixture was filtered through Celite and evaporated in vacuo to give an oil. Trituration of this oil with acetonitrile and filtration of the resulting solid gave 3.2 g of Compound 32. The filtrate was evaporated in vacuo and purified on SiO₂ eluting with 50% ethyl acetate in hexane to give an additional 1.75 g of product. (combined yield 79 %). ¹HNMR (CDCl₃) δ 8.44 (2H, d, J = 5.9 Hz), 7.22-6.71 (16H, m), 3.85 (2H, s), 2.63-2.57 (2H, m), 2.38-2.33 (2H, m), 1.61-1.49 (2H, m).

Compound 46

4-(4-fluorophenyl)-2-(3-hydroxypropyl)-3-(4-pyridyl)pyrrole

- 5 A solution of 2-(3-benzyloxypropyl)-4-(4-fluorophenyl)-3-(4-pyridyl)pyrrole (0.95 g, 0.0025 mol) in ethanol (125 mL) containing concentrated HCl (0.2 mL) was added to Pd on carbon (0.2 g). This mixture was placed in a hydrogen atmosphere for 16 hours on a Parr hydrogenator at 50 PSI. The mixture was filtered through Celite and triethylamine (0.5 mL) was added to the resulting
- 10 solution, followed by evaporation in vacuo to give a solid. The solid was extracted into ethyl acetate (100 mL) and washed with water (3 X 50 mL). The organics were dried over Na₂SO₄ and evaporated in vacuo to give a light yellow solid (0.7 g, 96% yield). ¹HNMR (DMSO-d₆) δ 11.10 (1H, s, NH), 8.44 (2H, d), 7.05 (6H, m), 6.91 (1H, d), 4.53 (1H, br s, OH), 3.49 (2H, br s), 2.64
- 15 (2H, t), 1.72 (2H, m).

Compound 47

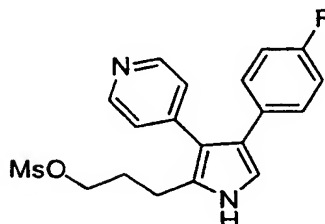


- 20 4-(4-fluorophenyl)-2-(3-morpholinopropyl)-3-(4-pyridyl)pyrrole
- 4-(4-fluorophenyl)-2-(3-mesyloxypropyl)-3-(4-pyridyl)pyrrole (0.25 g, 0.0007 mol) was refluxed for 16 hours in CH₂Cl₂ (50 mL) and morpholine (0.25 mL). The solution was cooled and diluted with CH₂Cl₂ (~100 mL), then washed with H₂O (3 X 50 mL). The organics were dried over Na₂SO₄ and evaporated in
- 25 vacuo to give an oil. This oil was purified on SiO₂ eluting with 10% MeOH in CH₂Cl₂ to give 4-(4-fluorophenyl)-2-(3-morpholinopropyl)-3-(4-pyridyl)pyrrole

isolated as a solid (0.088 g, 36 % yield). ¹HNMR (DMSO-d₆) δ 11.12 (1H, s, NH), 8.42 (2H, d), 7.05 (6H, m), 6.95 (1H, d), 3.55 (4H, t), 2.62 (2H, t), 2.29 (6H, m), 1.71 (2H, m).

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Compound 48



4-(4-fluorophenyl)-2-(3-mesyloxypropyl)-3-(4-pyridyl)pyrrole

4-(4-fluorophenyl)-2-(3-hydroxypropyl)-3-(4-pyridyl)pyrrole (0.55 g, 0.0019 mol) was combined with triethylamine (0.52 mL, 0.0037 mol) in CH₂Cl₂ (50 mL) and cooled to 10°C. Methanesulfonylchloride (0.16 mL, 0.0020 mol) was added dropwise and the resulting mixture was allowed to warm to room temperature. This mixture was diluted with CH₂Cl₂ (50 mL) and washed with water (30 mL). The organics were dried over Na₂SO₄ and evaporated *in vacuo* to give an oil. This oil was dissolved in EtOAc and purified through a bed of SiO₂ (~20 mL) eluting with EtOAc. Evaporation of the solvent *in vacuo* gave a yellow solid (0.63 g, 91% yield). ¹HNMR (DMSO-d₆) δ 11.25 (1H, s, NH), 8.45 (2H, d), 7.09 (6H, m), 6.94 (1H, d), 4.19 (2H, t), 3.17 (3H, s), 2.71 (2H, t), 1.98 (2H, m).

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III. Biological Assays and Activity

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A. p38 Inhibition In-Vitro Enzyme Assay

A solution (38 μL) of purified recombinant p38 (6xHis-p38 expressed in *E.coli*), myelin basic protein substrate (determined empirically), and a buffer of pH 7.5 (Hepes:25 mM, MgCl₂:10 mM, MnCl₂:10 mM) were added to 92 wells of a 96-well round bottom polypropylene plate. The amount of enzyme was determined empirically based on the linear range of the assay and the acceptable signal to noise ratio. The remaining wells were used for control ("CTRL") and background ("BKG"). The CTRL was prepared with the enzyme,

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substrate buffer and 2% DMSO, and the BKG was prepared with substrate buffer and 2% DMSO.

A solution (12 μ L) of the test compound in DMSO was added to the testing wells. Compounds were diluted to 125 μ M in 10% DMSO/H₂O and assayed at 25 μ M where the final DMSO concentration was 2%. The ATP/³³P-ATP solution (10 μ L containing 50 μ M unlabeled ATP and 1 μ Ci ³³P-ATP) was added to all wells and the completed plates were mixed and incubated at 30°C for 30 min. Ice-cold 50 % TCA/10 mM sodium phosphate (60 μ L) was added to each well and the plates were kept on ice for 15 min. The contents of each well were transferred to the wells of a 96-well filterplate (Millipore, MultiScreen-DP) and the filterplate was placed on a vacuum manifold fitted with a waste collection tray. The wells were washed five times with 10% TCA/10 mM sodium phosphate (200 μ L) under vacuum. MicroScint-20 scintillant was added, and the plates were sealed using Topseal-S sheets and counted in a Packard TopCount scintillation counter using a ³³P liquid program with color quench correction, where the output is in color quench-corrected cpm. The % inhibition of each test compound as shown in Table 2 was calculated by the following formula: % inhibition = [1- (sample -BKG)/(CTRL-BKG)] x 100.

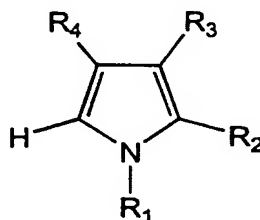


Table 2

Cpd.	R ₁	R ₂	R ₃	R ₄	% p38 inhib @ 10 μ M
2	CH ₃	H	4-pyr	3,4-F-Ph	15
3	4-NO ₂ -Ph	H	4-pyr	3,4-F-Ph	80
4	4-CN-Ph	H	4-pyr	3,4-F-Ph	21

14	CH ₃	H	4-pyr	3-OCH ₃ -Ph	43
18	4-CN-Ph	H	4-pyr	3-OCH ₃ -Ph	23
28	H	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	49
29	CH ₃	H	4-pyr	4-F-Ph	34
30	4-NO ₂ -Ph	H	4-pyr	4-F-Ph	70
31	4-NO ₂ -Ph	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	67
32	4-NHAc-Ph	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	38
33	4-NH ₂ -Ph	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	51

Although compounds were initially tested at 20 μ M, when warranted, the compounds were also tested at 4-fold increments above and below that concentration. In addition, the IC₅₀ was calculated for some compounds using the Deltagraph 4-parameter curve-fitting program.

B. In-Vitro Whole Cell Assay for TNF- α Inhibition

Freshly obtained venous blood was anticoagulated with heparin, diluted with an equal volume of phosphate buffered saline ("PBS") and placed in a sterile tube or other container. Aliquots (30 mL) of this mixture were transferred to centrifuge tubes which were underlaid with Ficoll-Hypaque (15 mL). The prepared tubes were centrifuged at 400 x g, without braking, for 30 min at room temperature. Approximately 1/2 to 2/3 of the platelet layer above the mononuclear cell band was removed with a pipette. The majority of the mononuclear cell layer was carefully removed using a pipette and these PBMC's were diluted with PBS and spun at 600 x g for 15 min. The resulting PBMC's were washed with another portion of PBS and spun at 400 x g for 10 min at room temperature. The recovered pellets were diluted in low endotoxin RPMI / 1% FCS culture medium, and gave a cell concentration of 0.5-2.0 X 10⁶ PMBC/ mL. A small volume of the suspension was removed for counting on a hemocytometer and the remaining preparation was centrifuged at 200 x g for 15 min at room temperature. The recovered pelleted PMBC's were resuspended in RPMI / 1% FCS to a concentration of 1.67 x 10⁶/mL.

To run the assay, the PBMC suspension (180 μ L) was transferred to duplicate wells of a 96-well flat-bottom microtiter plate and incubated for 1 h at 37°C. A solution of test compound (10 μ L: prepared at 20 x the desired final concentration) was added to each well and the plate was incubated for 1 h at 37°C. A solution (10 μ L) of LPS in RPMI / 1% FCS (200 ng/mL) was added and the wells were incubated overnight at 37°C. The supernate (100 μ L) was removed from each well and diluted with RPMI / 1% FCS (400 μ L). The samples were analyzed for TNF- α using a commercial ELISA kit (Genzyme).

Select compounds of the invention are listed in Table 3. The compounds were tested for their ability to inhibit TNF- α production. The IC₅₀ nM results are listed for the indicated compounds.

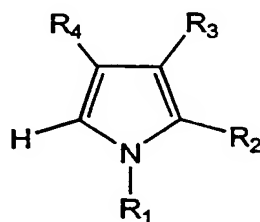


TABLE 3

Cpd.	R ₁	R ₂	R ₃	R ₄	TNF- α	
					IC ₅₀ nM	Scheme
1	H	H	4-pyr	3,4-F-Ph	20	2
2	CH ₃	H	4-pyr	3,4-F-Ph	30	1
3	4-NO ₂ -Ph	H	4-pyr	3,4-F-Ph	2	4
4	4-CN-Ph	H	4-pyr	3,4-F-Ph	2	4
5	4-CH ₃ SO ₂ -Ph	H	4-pyr	3,4-F-Ph	30	4
6	CH ₃	H	4-pyr	3,5-F-Ph	175	1
7	CH ₃	H	4-pyr	3-CF ₃ ,4-F-Ph	100	1
8	CH ₃	H	4-pyr	3-CF ₃ ,5-F-Ph	1500	1
9	CH ₃	H	4-pyr	3-CF ₃ -Ph	125	1
10	CH ₃	H	4-pyr	3-F-Ph	125	1
11	CH ₃	H	4-pyr	3-NO ₂ -Ph	100	1
12	H	H	4-pyr	3-OH-Ph	300	2

13	H	H	4-pyr	3-OCH ₃ -Ph	55	2
14	CH ₃	H	4-pyr	3-OCH ₃ -Ph	55	1
15	4-NO ₂ -Ph	H	4-pyr	3-OCH ₃ -Ph	20	4
16	4-NHAc-Ph	H	4-pyr	3-OCH ₃ -Ph	75	4
17	4-NH ₂ -Ph	H	4-pyr	3-OCH ₃ -Ph	95	4
18	4-CN-Ph	H	4-pyr	3-OCH ₃ -Ph	15	4
19	4-CH ₃ SO ₂ -Ph	H	4-pyr	3-OCH ₃ -Ph	30	4
20	2-pyr	H	4-pyr	3-OCH ₃ -Ph	150	4
21	2,4-NO ₂ -Ph	H	4-pyr	3-OCH ₃ -Ph	80	4
22	4-SO ₂ -Ph	H	4-pyr	3-OCH ₃ -Ph	1000	4
23	(CH ₂) ₃ -Ph	H	4-pyr	3-OCH ₃ -Ph	2000	4
24	H	H	4-pyrimidine	3-OCH ₃ -Ph	250	2
25	CH ₃	H	4-pyr	3-thienyl	900	1
26	CH ₃	H	4-pyr	4-OCH ₃ -Ph	2000	1
27	H	H	4-pyr	4-F-Ph	90	2
28	H	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	3.5	3
29	CH ₃	H	4-pyr	4-F-Ph	200	1
30	4-NO ₂ -Ph	H	4-pyr	4-F-Ph	2	4
31	4-NO ₂ -Ph	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	15	4
32	4-NHAc-Ph	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	5	5
33	4-NH ₂ -Ph	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	8	5
34	CH ₃	H	4-pyr	4-pyr	3000	1
35	CH ₃	H	4-pyr	4-SCH ₃ -Ph	250	1
36	CH ₃	H	4-pyr	4-(CH ₃) ₂ N-Ph	500	1
37	CH ₃	H	4-pyr	4-SOCH ₃ -Ph	3000	1
38	CH ₃	H	4-pyr	Ph	350	1
39	(CH ₂) ₃ N(CH ₂) ₅	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	5	4
40	(CH ₂) ₂ N(CH ₂) ₅	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	3	4
41	(CH ₂) ₂ CH(CH ₂) ₃ NCH ₃	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	5	4
42	(CH ₂) ₂ CH(CH ₂) ₃ NCH ₃ CH ₂	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	2	4
43	(CH ₂) ₂ N(CH ₂) ₂ O(CH ₂) ₂	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	1	4
44	(CH ₂) ₃ N(CH ₃) ₂	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	8	4
45	(CH ₂) ₂ N(CH ₂) ₄	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	3	4
46	H	(CH ₂) ₃ -OH	4-pyr	4-F-Ph	544	6
47	H	(CH ₂) ₂ N(CH ₂) ₂ O(CH ₂) ₂	4-pyr	4-F-Ph	177	6

C. In Vivo Rodent Assay for Inhibition of TNF- α Production

The ability of the instant compounds to inhibit LPS-induced TNF- α production was demonstrated in the following in vivo rodent assays. Mice (BALB / cJ females, Jackson Laboratories) or rats (Lewis males, Charles River) were fasted for 30 min prior to oral dosing with 5-10 mL/kg of test compound at 5-50 mg/kg. Thirty minutes after dosing, the animals were injected intraperitoneally with LPS at 1 mg/kg and returned to their cages for 1 h. Animals were anesthetized by CO₂, exsanguinated by cardiac puncture and whole blood collected (0.1 - 0.7 mL). The blood was allowed to clot and serum was transferred to a centrifuge tube. This sample was centrifuged, and serum was collected, aliquoted and frozen at -80°C. Samples were tested by commercial ELISA's for TNF- α (Endogen for mouse TNF- α and Biosource for rat TNF- α). The in vivo test results for select compounds of the invention are listed in Table 4. The compounds were tested for their ability to inhibit TNF- α production in mice and the data are listed as % inhibition at 25 mg/kg.

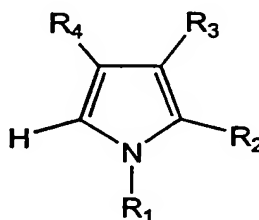


TABLE 4

Cpd.	R1	R2	R3	R4	TNF- α % Inhibition Mouse
1	H	H	4-pyr	3,4-F-Ph	96
7	CH ₃	H	4-pyr	3-CF ₃ ,4-F-Ph	79
11	CH ₃	H	4-pyr	3-NO ₂ -Ph	94

14	CH ₃	H	4-pyr	3-OCH ₃ -Ph	71
16	4-NHAc-Ph	H	4-pyr	3-OCH ₃ -Ph	50
17	4-NH ₂ -Ph	H	4-pyr	3-OCH ₃ -Ph	66
18	4-CN-Ph	H	4-pyr	3-OCH ₃ -Ph	60
19	4-CH ₃ SO ₂ -Ph	H	4-pyr	3-OCH ₃ -Ph	-127
27	H	H	4-pyr	4-F-Ph	100
28	H	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	10
30	4-NO ₂ -Ph	H	4-pyr	4-F-Ph	53
39	(CH ₂) ₃ N(CH ₂) ₅	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	100
40	(CH ₂) ₂ N(CH ₂) ₅	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	96
41	(CH ₂) ₂ CH(CH ₂) ₃ NCH ₃	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	100
42	(CH ₂) ₂ CH(CH ₂) ₃ NCH ₃ CH ₂	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	100
43	(CH ₂) ₂ N(CH ₂) ₂ O(CH ₂) ₂	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	93
44	(CH ₂) ₃ N(CH ₃) ₂	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	100
45	(CH ₂) ₂ N(CH ₂) ₄	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	99
47	H	(CH ₂) ₂ N(CH ₂) ₂ O(CH ₂) ₂	4-pyr	4-F-Ph	77

The in vivo test results for select compounds of the invention are listed in Table 5. The compounds were tested for their ability to inhibit TNF- α production in mice and the data are listed as % inhibition at 10 mg/kg.

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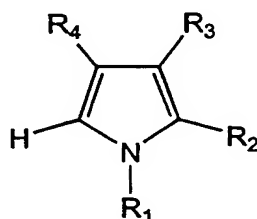


TABLE 5

Cpd.	R1	R2	R3	R4	TNF- α % Inhibition Mouse
3	4-NO ₂ -Ph	H	4-pyr	3,4-F-Ph	81
7	CH ₃	H	4-pyr	3-CF ₃ ,4-F-Ph	61
11	CH ₃	H	4-pyr	3-NO ₂ -Ph	74

14	CH ₃	H	4-pyr	3-OCH ₃ -Ph	41
18	4-CN-Ph	H	4-pyr	3-OCH ₃ -Ph	24
27	H	H	4-pyr	4-F-Ph	73
28	H	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	10
31	4-NO ₂ -Ph	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	47
32	4-NHAc-Ph	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	48
39	(CH ₂) ₃ N(CH ₂) ₅	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	36
40	(CH ₂) ₂ N(CH ₂) ₅	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	96
41	(CH ₂) ₂ CH(CH ₂) ₃ NCH ₃	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	100
42	(CH ₂) ₂ CH(CH ₂) ₃ NCH ₃ CH ₂	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	100
43	(CH ₂) ₂ N(CH ₂) ₂ O(CH ₂) ₂	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	93
44	(CH ₂) ₃ N(CH ₃) ₂	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	100
45	(CH ₂) ₂ N(CH ₂) ₄	(CH ₂) ₃ -Ph	4-pyr	4-F-Ph	99

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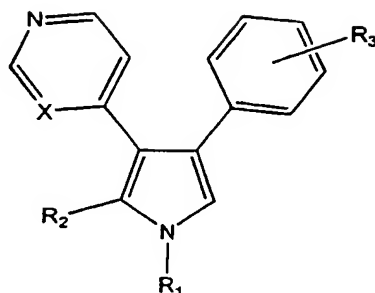
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What is claimed is:

1. A compound having the structure:

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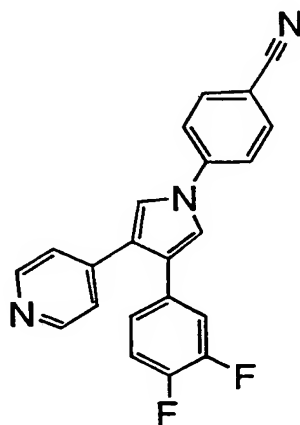
or a pharmaceutically acceptable salt thereof, wherein:

- (a) R_1 is selected from the group consisting of (i) hydrogen, (ii) C_{1-5} alkyl, (iii) substituted or unsubstituted C_{1-5} alkylamino, (iv) N-containing C_{1-5} alkyl heterocycle selected from thiazolidine, piperidine, morpholine, piperazine, thiomorpholine, pyrrolidine, thiazine, pyrrole and imidazole, (v) phenyl, (vi) phenyl independently substituted with one or more of C_{1-5} alkyl, amino, substituted amino, nitro, nitrile and sulfone, and (vii) pyridine;
- (b) R_2 is selected from the group consisting of (i) hydrogen, (ii) $(CH_2)_3OH$, (iii) substituted or unsubstituted C_{1-5} alkyl phenyl, and (iv) N-containing C_{1-5} alkyl heterocycle selected from thiazolidine, piperidine, morpholine, piperazine, thiomorpholine, pyrrolidine, thiazine, pyrrole and imidazole;
- (c) R_3 is one or more substituents independently selected from the group consisting of hydrogen, halogen, methoxy, nitro, trifluoromethyl, hydroxy, dimethylamino and methylsulfoxide; and
- (d) X is either C or N.

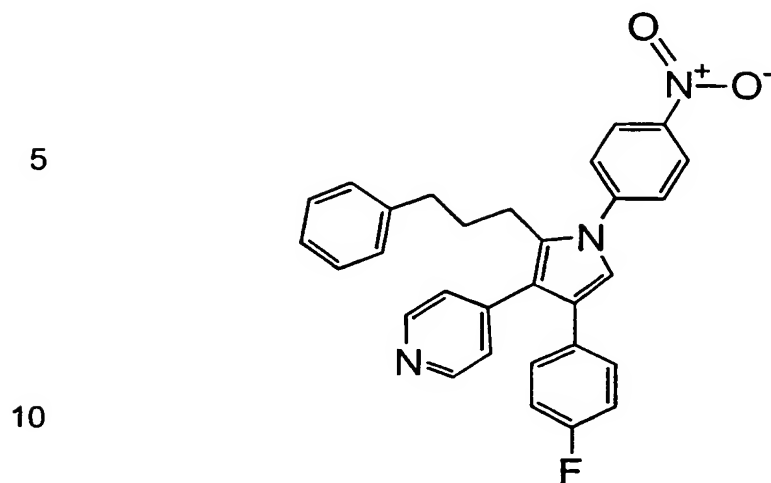
2. The compound of claim 1, wherein:

- (a) R_1 is selected from the group consisting of (i) hydrogen, (ii) C_{1-5} alkyl, (iii) substituted or unsubstituted C_{1-5} alkylamino, (iv) N-containing C_{1-5} alkyl heterocycle selected from piperidine, morpholine and pyrrolidine, and (v) phenyl substituted with a substituent selected from the group consisting of amino, substituted amino, nitro and nitrile;
- (b) R_2 is selected from the group consisting of hydrogen and $(CH_2)_3$ phenyl;
- (c) R_3 is selected from the group consisting of halogen, nitro and trifluoromethyl; and
- (d) X is C.

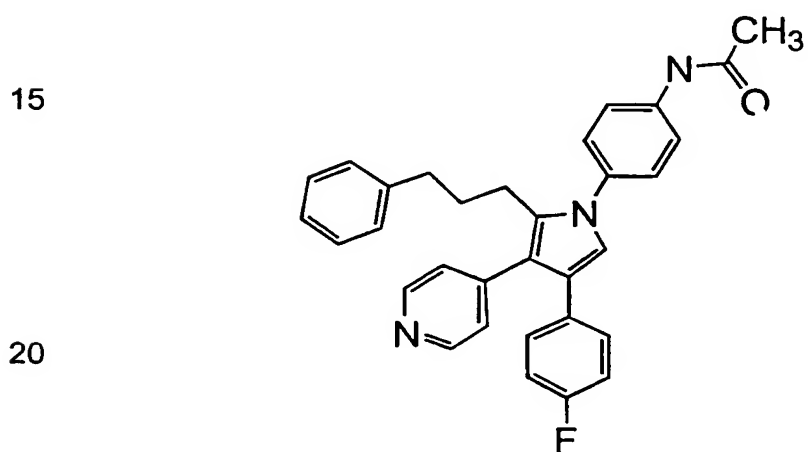
3. The compound of claim 1 having the structure:



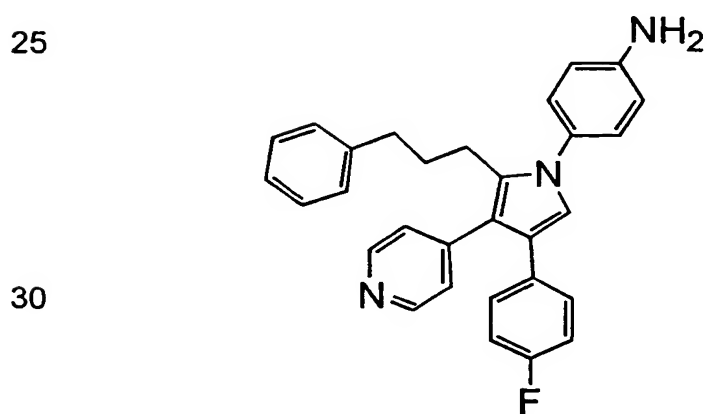
4. The compound of claim 1 having the structure:



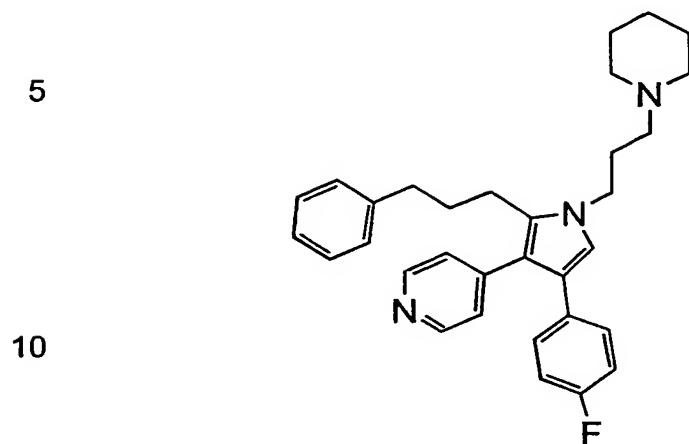
5. The compound of claim 1 having the structure:



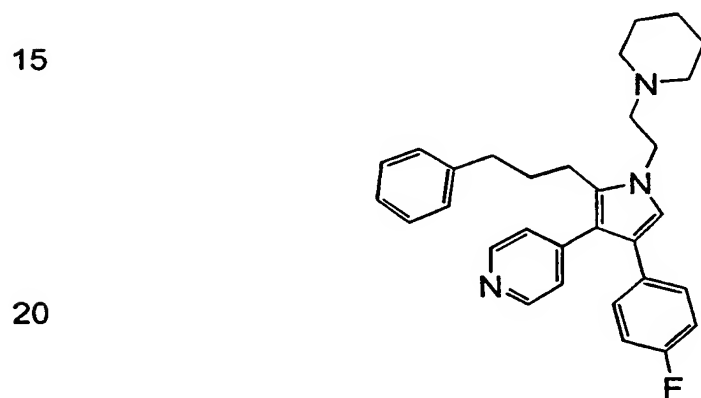
6. The compound of claim 1 having the structure:



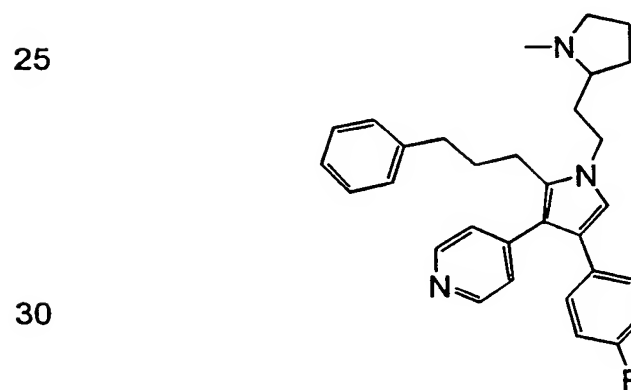
7. The compound of claim 1 having the structure:



8. The compound of claim 1 having the structure:

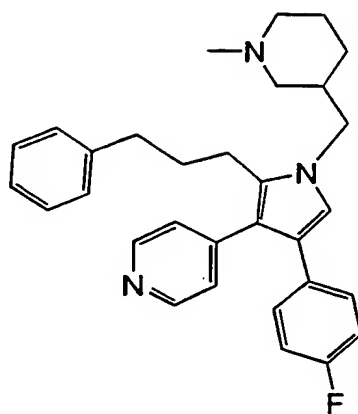


9. The compound of claim 1 having the structure:



10. The compound of claim 1 having the structure:

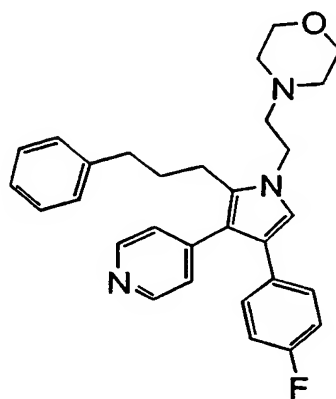
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11. The compound of claim 1 having the structure:

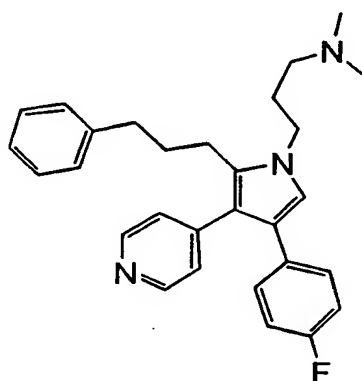
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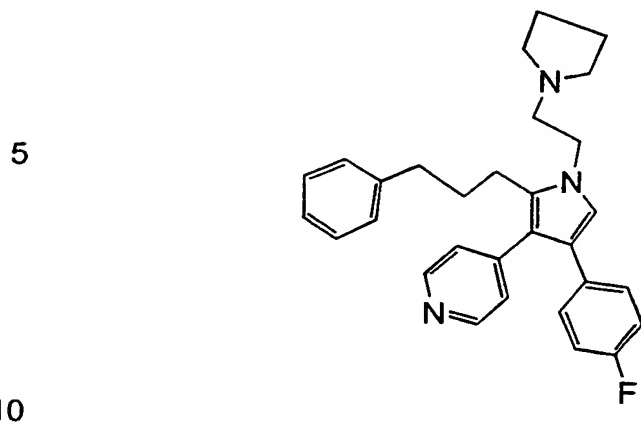
12. The compound of claim 1 having the structure:

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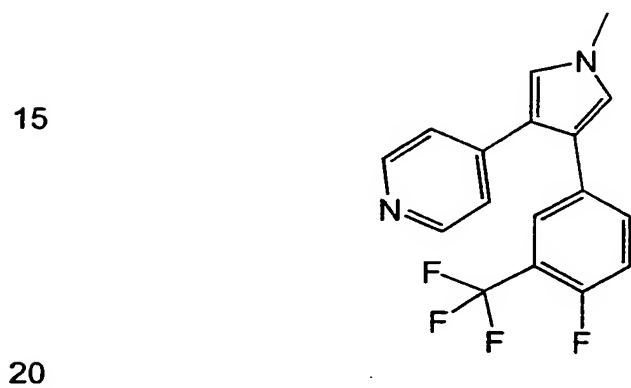


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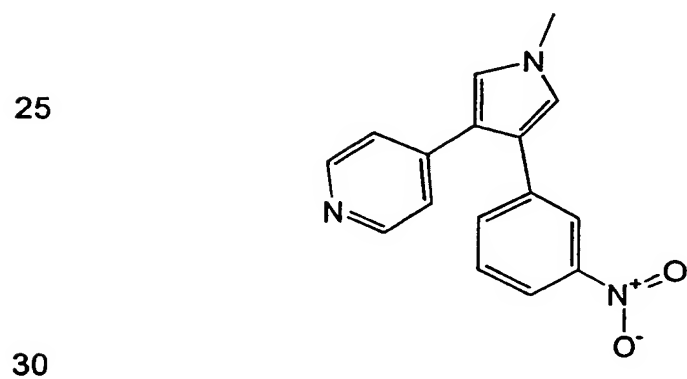
13. The compound of claim 1 having the structure:



14. The compound of claim 1 having the structure:

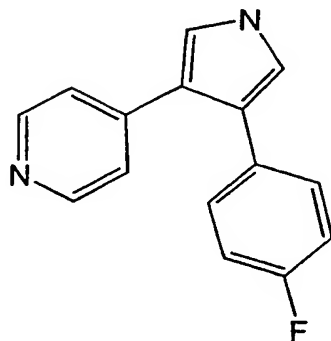


15. The compound of claim 1 having the structure:



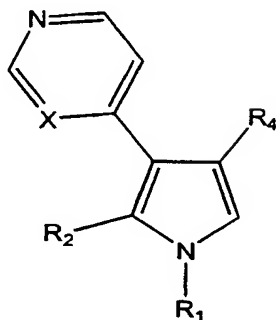
16. The compound of claim 1 having the structure:

5



17. A compound having the structure:

15



or a pharmaceutically acceptable salt thereof, wherein:

20

- (a) R_1 is selected from the group consisting of (i) hydrogen, (ii) C_{1-5} alkyl, (iii) substituted or unsubstituted C_{1-5} alkylamino, (iv) N-containing C_{1-5} alkyl heterocycle selected from thiazolidine, piperidine, morpholine, piperazine, thiomorpholine, pyrrolidine, thiazine, pyrrole and imidazole, (v) phenyl, (vi) phenyl independently substituted with one or more of C_{1-5} alkyl, amino, substituted amino, nitro, nitrile and sulfone, and (vii) pyridine;

25

- (b) R_2 is selected from the group consisting of (i) hydrogen, (ii) $(CH_2)_3OH$, (iii) substituted or unsubstituted C_{1-5} alkyl phenyl, and (iv) N-containing C_{1-5} alkyl heterocycle selected from thiazolidine, piperidine, morpholine, piperazine, thiomorpholine, pyrrolidine, thiazine, pyrrole and imidazole;

30

- (c) R_4 is a substituted or unsubstituted heterocycle selected from pyridine, pyrimidine, furan or thiophene; and,
- (d) X is either C or N.
- 5 18. The compound of claim 17, wherein:
- (a) R_1 is selected from the group consisting of (i) C_{1-5} alkyl, (ii) substituted or unsubstituted C_{1-5} alkylamino, (iii) substituted or unsubstituted C_{1-5} alkyl heterocyclic amino, (iv) phenyl, and (v) phenyl independently substituted with one or more of amino, substituted amino, nitro or nitrile;
- 10 (b) R_2 is selected from the group consisting of hydrogen and $(CH_2)_3$ phenyl; and
- (c) X is C.
- 15 19. A pharmaceutical composition comprising the compound of claim 1 or claim 17 and a pharmaceutically acceptable carrier.
20. A method of treating a subject having a disorder ameliorated by reducing TNF- α production and/or p38 activity in appropriate cells, which comprises administering to the subject a therapeutically effective dose of the pharmaceutical composition of claim 19.
- 20 21. The method of claim 20, wherein the disorder is an inflammatory disorder.
- 25 22. The method of claim 20, wherein the disorder is selected from the group consisting of rheumatoid arthritis, osteoporosis, osteoarthritis, allergic inflammation, periodontal disorder, inflammatory bowel disorder, septic shock, insulin-dependent diabetes mellitus, non-insulin-dependent diabetes, cachexia, pulmonary fibrosis, myasthenia gravis, Crohn's disease, hepatitis, primary biliary cirrhosis, acute pancreatitis, allograft rejection, glioblastoma, alopecia areata, psoriasis, ischemia, congestive
- 30

- 5 heart failure, restenosis, atherosclerosis, systemic lupus erythematosus, nephritis, Guillain-Barre Syndrome, viral myocarditis, HIV replication, T-cell depletion in HIV infection, cognitive deficits induced by neuronal inflammation, multiple sclerosis, stroke, neuropathic pain, HIV dementia and Alzheimer's disease.
23. The method of claim 22, wherein the disorder is rheumatoid arthritis.
- 10 24. A method of preventing an inflammatory response in a subject, comprising administering to the subject a prophylactically effective amount of the pharmaceutical composition of claim 19 either preceding or subsequent to an event anticipated to cause the inflammatory response in the subject.
- 15 25. The method of claim 24 wherein the event is selected from the group consisting of an insect sting and an animal bite.

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INTERNATIONAL SEARCH REPORT

Inte. ial Application No
PCT/US 00/11531

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/04 A61K31/4427 A61K31/506 A61P29/00 C07D401/14
C07D403/04 C07D409/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 02430 A (SAKAKIBARA MINORU ;PFIZER PHARMA (JP); KAWAI AKIYOSHI (JP); KAWAI) 22 January 1998 (1998-01-22) page 1, line 7 - line 30 page 6, line 19 - line 22 examples 25,30,42,44,51,52	1-25
A	WO 97 05877 A (MERCK & CO INC ;LASZLO STEPHEN E DE (US); MANTLO NATHAN B (US); PO) 20 February 1997 (1997-02-20) cited in the application page 1, line 11 - line 20 examples 1,28,30,61	1-25
A	WO 97 16442 A (MERCK & CO INC ;LASZLO STEPHEN E DE (US); CHANG LINDA L (US); KIM) 9 May 1997 (1997-05-09) examples 16,121,176,274,276	1-25
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

14 August 2000

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